Tryptophan 2,3-dioxygenase (TDO) inhibitors : Identification of new scaffolds using virtual screening

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SYNTHESIS, STRUCTURAL AND ENZYMATIC STUDY OF VINYL-1H-INDOLE ANALOGUES AS POTENTIAL INHIBITORS OF TRYPTOPHAN 2,3- DIOXYGENASE (TDO), A TARGET IN ANTICANCER IMMUNOTHERAPY

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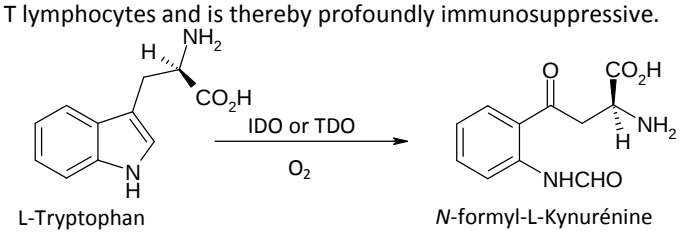
Immunotherapy is a promising novel strategy for cancer therapy. It consists of the therapeutic vaccination of cancer patients to stimulate their (natural) immune system against cancer cells. This approach, however, showed limited efficacy in vivo. Cancer cells are actually able to develop enzymatic mechanisms allowing tumours to resist or escape the immune rejection. Among the enzymes involved, the indoleamine 2,3-dioxygenases IDO and TDO represents potential actors.[1-3] These enzymes catalyse the rapid degradation of tryptophan (Trp) through the kynurenine (KYN) pathway to form quinolinic acid (QA). This results in a local Trp depletion that severely affects the proliferation of T lymphocytes and is thereby profoundly immunosuppressive.



L-Tryptophan — *N*-formyl-L-Kynurénine

Figure: Metabolism of L-tryptophan to *N*-formyl-L-kynurenine catalyzed by IDO or TDO.

This project was funded in part by Télévie (FNRS grant 7.4.543.07) and led in collaboration with the team of Pr Benoit Van Den Eynde (LICR, UCL) and Pr Moreno Galeni (CIP, ULG) aims at developing novel TDO inhibitors using a rational approach. These inhibitors will allow a better understanding of the role of TDO in the phenomenon of immunosuppression, especially in cancerous tumors.

A series of vinyl-1H-indoles has been synthesized and their inhibitory potential has been evaluated on TDO of *Ralstonia metallidurans* (rmTDO) overexpressed in *E.coli* and purified by affinity chromatography. Crystallographic structure of some analogues was obtained and used as starting point for a docking study of these inhibitors in a model of humanized rmTDO. These data allowbetter understanding of how this family of inhibitors interact with TDO. This process is presented on this poster.

References:

1) Uyttenhove, C., and *al.*,(2003), **Nat Med** ,9,1269-1274
2) Van den Eynde, B., and *al.*, (2009), U.S. application S.N.:61/247,372.
3) Batabyal D. and *al.*,(2007), **JACS** ,129, 15690-15701